CASE REPORT

ANCA negative eosinophilic granulomatosis with polyangiitis: sometimes it really IS vasculitis

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SUMMARY

A 21-year-old woman, with a background of asthma, presented to medical admissions ward, with diarrhoea and vomiting; the clinical picture during her admission evolved to include acute shortness of breath, seizures, unsteadiness, low mood and apathy. Investigations revealed pericardial, pleural effusions, myocardial infiltration and vasculitic lesions in the brain. Although serological tests for autoantibodies were negative, an eventual diagnosis of eosinophilic granulomatosis with polyangiitis, formerly known as Churg-Strauss syndrome, was performed based on the clinical picture. The multiorgan involvement meant that the initial diagnosis and effective management required multidisciplinary input from cardiology, neurology, rheumatology, psychiatry, immunology and occupational and physiotherapy.

BACKGROUND

This is an important case not only due to its complexity in terms of diagnosis but also owing to its rapid progression involving multiple systems. This posed diagnostic difficulties and a multidisciplinary approach was required at all stages of management. Our patient clinically presented with signs and symptoms suggestive of gastrointestinal, pulmonary, cardiac and neurological disorders. Eosinophilic granulomatosis with polyangiitis (EGPA) would have been an easier diagnosis to make from the offset if there was a typical skin rash, asthma exacerbation and/or if, serologically, antineutrophil cytoplasmic antibody (ANCA) was positive. ANCA negative EGPA requires piecing together different aspects of the clinical picture as the autoantibody tests will be negative. It is important to bear this diagnosis in mind for complex cases and also to understand the broad management plan required in managing such a systemic illness and ensuring the correct specialists are involved.

CASE PRESENTATION

A 21-year-old woman, with a history of childhood asthma, was admitted to the medical admissions unit in a district general hospital, with a 2-week history of abdominal pain, diarrhoea and vomiting. She was found to have elevated inflammatory markers and a significantly elevated eosinophil count (figure 1 for full investigation results). Initial chest and abdominal X-rays were normal. She went on to have a CT scan of her chest, abdomen and pelvis, which revealed a normal abdomen, but a moderate pericardial effusion with evidence of

myocarditis and left lung consolidation, and bilateral pleural effusions (figure 2).

Initially suspecting a chest infection, the patient was started on broad spectrum antibiotics. An immunological screen was also sent at this time. To investigate the pericardial effusion, an echocardiogram was performed. This revealed the fluid to be mostly posterior and, therefore, due to technical difficulties, pericardiocentesis was not carried out. Additionally, the patient's ejection fraction was found to be only 35%. Over the next few days, she became progressively more short of breath and required a transfer to ITU for intubation. A repeat chest X-ray (figure 3) showed progression of the pleural effusions, which were drained and found to be transudates in keeping with cardiac failure. The patient was reviewed by the cardiologist and started on treatment for heart failure, with bisoprolol, ramipril and furosemide. At this stage, she was reviewed by the rheumatologist and the pathology was labelled as 'autoimmune', although no autoantibody results were available. For this, she was started on intravenous methylprednisolone 500 mg once a day for 3 days.

She was eventually extubated and transferred to a base ward. She was started on a reducing dose of oral steroids for suspected hypereosinophilic syndrome, as the final autoimmune screen was negative. Her eosinophil count did respond to the steroid treatment and was normal within 2 weeks. She also clinically stabilised on heart failure therapy, and a repeat echo showed a stable pericardial effusion. However, 2 weeks later, the patient developed acute confusion, and went on to have three seizures. She was also started on levetiracetam to control her seizure activity. Initial CT of the head, lumbar puncture and EEG were normal, but MRI and MR angiogram scans revealed deep white matter changes, in keeping with cerebral vasculitis. The patient also displayed neuropsychiatric manifestations with blank facial expression, paucity of speech, reduced cognition and apathy. A week after the initial seizure, with the added results, the case was rediscussed with the rheumatology and immunology teams, who believed that, based on the clinical findings and blood results, this was highly suspicious for ANCA-negative EGPA; the patient was immediately started on a cyclophosphamide and high-dose steroid regime.

To help exclude other causes of her initial eosinophilia, the patient went on to have a bone marrow biopsy, which demonstrated hypocellular marrow secondary to the steroid suppression and was not diagnostically significant.

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Figure 1 Relevant significant results in table format. ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; CXR, chest X-ray.

Relevant Investigations	Results
Full blood count	Eosinophils 11.5 (0.0-0.5 10 ⁹ /L)
C-reactive protein	165 (<5 mg/L)
Urea & electrolytes	Normal
Liver function tests	Normal
ANA/ANCA/Mitochondrial/Smooth Muscle Antibodies	Negative
Serum IgE	>5000 kU/L
HIV	Negative
Urine/stool/blood cultures	Negative
Initial CXR on Admission	Normal
CT Chest abdomen and Pelvis	Bilateral pleural effusions, pericardial effusion and myocarditis
CXR 1 week post admission	Progressive bilateral pleural effusions and cardiomegaly
CT head post seizures	Normal
MRI head with contrast	Areas of deep white matter changes consistent with vasculitis

The patient improved with the above regime and, with occupational and physiotherapy input, was able to progress with her mobility. She was also reviewed by the psychiatry team, who advised citalopram for her mood. She had a cardiac MRI (cMRI) performed 3 months after her initial admission, which demonstrated an improved ejection fraction and a reduction in the pericardial effusion. Twelve months after the initial diagnosis, she remains under the neurology, rheumatology, cardiology, immunology and psychiatry teams, but her symptoms have remained under control.

DIFFERENTIAL DIAGNOSIS

A wide array of differential diagnoses was considered in this case as the clinical picture progressed. Initially, our patient was admitted with suspected gastroenteritis, which then progressed to suspected myocarditis/pericarditis with pulmonary infection after her CT of the chest, abdomen and pelvis. Cardiac involvement progressed with a reduced ejection fraction and worsening heart failure. An autoimmune cause was considered from this stage onwards—possibly hypereosinophilic syndrome. However, with the neurological involvement and evidence of cerebral vasculitis, the clinical picture materialised as ANCA negative EGPA with *end organ damage*.

Figure 2 CT of the thorax demonstrating pericardial effusion and pleural effusions.

TREATMENT

The patient was started on intravenous antibiotics in the first instance, but as her heart failure progressed, she was managed with diuretics, β blockers and ACE-inhibitors. With the suspicion of hypereosinophilic syndrome, she was given intravenous methylprednisolone and started on a reducing dose of steroids. As the clinical picture progressed with neurological involvement, the diagnosis of ANCA negative EGPA was made. As our patient had generalised disease with multiorgan involvement, she was started on cyclophosphamide infusion at a dose of 15 mg/kg, with 3 weeks in between each infusion. In total, she had five infusions of this, together with high-dose prednisolone—this helped induce remission—and she was then started on a maintenance dose of azathioprine.

OUTCOME AND FOLLOW-UP

At writing, 12 months after her discharge, the patient is still under regular review by different specialities, but her symptoms have been under control and she has not had any flare ups of her vasculitis.

Figure 3 Chest X-ray demonstrating bilateral pleural effusions and cardiomegaly.

Her neurological and neuropsychiatric symptoms significantly improved, and her cMRI showed an improved ejection fraction from <35% to 56%, which reflected her stabilised cardiac symptoms, although her exercise tolerance is still limited to a 100 yards. Chest X-ray (performed 3 months after) also showed an improvement (figure 4).

DISCUSSION

EGPA is a rare multisystem, small vessel vasculitis. Prevalence ranges from between 10.7 and 14 per million inhabitants.^{1 2} Churg and Strauss² defined the involvement of allergic granulomatosis, allergic angiitis and periarteritis nodosa as a clinical syndrome consisting of severe asthma, fever and hyper eosinophilia together with vascular injury in different organs. Eosinophils contain toxic inflammatory mediators that owe to the devastating injury of organs. EGPA is an ANCA-associated vasculitis, more specifically, a myeloperoxidase-ANCA (MPO-ANCA). However, it is only found in 40% of cases, which is less than other ANCA-related conditions.^{3–6}

The pathogenesis of EGPA is unclear, however, there is a genetic and immunological basis. HLA-DRB1*04 and *07 alleles and the related HLADRB4 gene are associated with an increased risk of developing EGPA.⁷ The release of cytokines from Th2-lymphocytes, and the eosinophilic release of basic and cationic protein, neurotoxin and peroxidase, induce endothelial damage and engage the oxidative stress cascade. Immunoglobulin E (IgE) has also been shown to promote eosinophilic vasculitis. It has been postulated that the presence of MPO-ANCA may correlate with more severe and aggressive forms of the disease. Triggers in patients who achieve good asthmatic control with antiasthmatic medications such as leucotriene modifying agents, can reveal an underlying systemic inflammatory process—EGPA.^{8 9}

In 1984, Lanham *et al*¹⁰ set out the criteria for diagnosing EGPA, these include: asthma, eosinophilia and vasculitic involvement of two or more organs. The American College of Rheumatology requires four or more of the following for classifying vasculitis as EGPA: asthma, peripheral blood eosinophilia (more than 10% on differential white cell count), neuropathy, pulmonary infiltrates, paranasal abnormalities and extravascular eosinophilia.^{6 11 12}

Figure 4 Repeat chest X-ray 3 months after initial, demonstrating improvement.

Guillemin *et al* described the ‘five-factor score’ (FFS) which is associated with poor prognosis and higher mortality. The five parameters include: proteinuria—greater than 1 g/day, serum creatinine greater than 140 µmol/L, cardiomyopathy, and involvement of the gastrointestinal tract and the central nervous system.¹³ All patients with FFS ≥1 should receive immunosuppression (other than corticosteroids).^{13–16}

EGPA has three distinct phases, which usually follow chronologically: a prodromic phase with asthma and allergic manifestations; eosinophilic infiltration; and a systemic phase affecting the lungs and extrapulmonary manifestations such as kidneys, and gastrointestinal and central nervous systems.¹⁷ Zwerina *et al*¹⁸ recognised that EGPA in children frequently presented with pulmonary infiltrates and cardiac disease, whereas in adults, peripheral nerve and musculoskeletal symptoms predominated.^{6 19}

Our patient presented with non-specific diarrhoea and vomiting, which manifested into cardiac (pericardial effusion and myocarditis) and, eventually, neurological (seizures with cortical lesions) involvement, and psychiatric symptoms of abnormal behaviour and apathy. On further investigation, there was evidence of eosinophilia, and ANCA was negative with a history of asthma. This is in keeping with ANCA negative EGPA presenting more frequently in younger patients, as described by Zwerina *et al*.¹⁸

Treatment of EGPA involves use of immunosuppressive therapies such as cyclophosphamide—which induce remission—and concomitant use of corticosteroids.²⁰ Once remission is achieved, less cytotoxic immunosuppressants can be used, such as azathioprine or methotrexate, as maintenance. Use of monoclonal antibodies such as rituximab has also been reported.¹

On making the diagnosis of EGPA, and due to a high FFS score, our patient was started on cyclophosphamide in addition to prednisolone.^{15 21} Unfortunately, due to diagnostic uncertainty, there was almost a 5-week delay from admission in starting our patient on the correct treatment. Failure to act promptly with immunosuppression can accelerate end-organ damage, which can be irreversible and devastating. Use of immunosuppressants is usually long term, as patients can relapse.⁶

EGPA requires a multidisciplinary approach to manage patients appropriately and in a timely manner. In our case, the patient was under the care of cardiology, neurology, rheumatology and psychiatry, even as an outpatient. Follow-up is usually over several months or years and patients can have relapses requiring acute medical input.^{1 6 12 22 23}

Cardiac involvement in EGPA is more prevalent in patients with ANCA negative status.^{12 24} It has been extensively researched in recent years with the advent of cMRI techniques, which have aided the possibility of diagnosing early cardiac involvement. Cardiac manifestations include myocarditis, pericarditis, heart failure, myocardial infarction, pericardial effusion, valvular abnormalities and cardiac tamponade.¹⁴ At diagnosis, cardiac involvement may be clinically silent or not detected on ECHO; however, cMRI can identify microvasculitis or endocardial inflammation—largely due to eosinophilic infiltration.^{1 23} Use of non-corticosteroid immunosuppressives such as cyclophosphamide has been shown to limit cardiac damage and to improve cardiac function. Effectiveness depends on the duration of immunosuppressive usage.²⁵ Cardiology input was required for managing the heart failure of our patient. This was achieved using β blockers, ACE-inhibitors and diuretics, and by monitoring her renal function.

Neuropathy is frequently described in the literature as occurring in around 70% of cases.^{12 26} Owing to the eosinophilic

infiltration and the release of toxic mediators, this leads to small vessel arteritis of peripheral nerves. This burden leads to ischaemia and necrotising vasculitis of the nutrient vessels of nerves.^{12–26} Our patient did not exhibit evidence of peripheral neuropathy, however, she did present with central nervous system (CNS) disturbances—seizures and psychiatric disturbances. MRI of the head showed evidence of cerebral vasculitis. CNS involvement in EGPA is reported to be around 10%.¹² Our patient was managed with antiepileptic medications and under specialist neurological input. We attribute this to be due to vasculitic changes noted on the MRI of the patient's head.

In conclusion, we present a 21-year-old woman who presented with ANCA negative eosinophilic granulomatosis and polyangiitis. This disease has been researched extensively recently, however, its variable presentation can pose diagnostic difficulties. Therefore, our aim with this case report was to demonstrate how different specialities contributed to the management of this rare but potentially devastating multisystem disease.

Learning points

- ▶ Eosinophilic granulomatosis with polyangiitis is a rare multisystem vasculitis that can affect young patients.
- ▶ Early diagnosis is pertinent to preventing devastating progression of the disease.
- ▶ Corticosteroids are the mainstay of treatment, and cyclophosphamide should be initiated without delay in patients presenting with five-factor score ≥ 1 .
- ▶ Multidisciplinary input is essential for managing the patient.

Competing interests None declared.

Patient consent Obtained.

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